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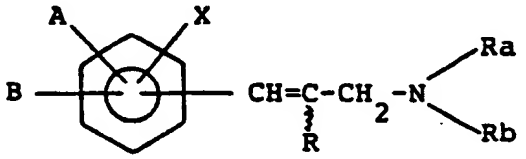
(54) Cinnamyl amines, process for their preparation and pharmaceutical compositions containing them.

(57) Compounds of formula I



(I)

wherein X is an amino or hydroxy group;

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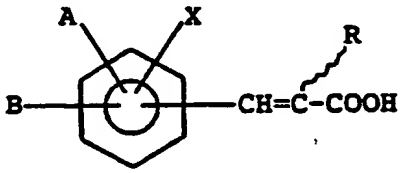
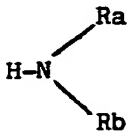
A and B being the same or different are hydrogen, alkyl, alkoxy, halogen or amino, or aminomethylene groups, when amino groups are alifatic or derived from nitrogen heterocycles;
R is hydrogen, lower alkyl, a cyano or free or esterified carboxyl;
Ra and Rb are alkyl groups, eventually substituted by Cl or OH, cycloalkyls, arylalkyls, heterarylalkyls, or if taken together with the nitrogen atom to which the are bound, they form a saturated or unsaturated heterocyclic ring.
Compounds I, that are prepared by reacting acids II



(II)

with amine III



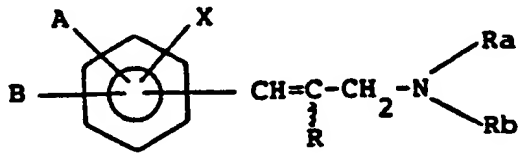
(III)

and formaldehyde have useful therapeutical properties.

CINNAMILAMMINES, PROCESS FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

The present invention relates to cynnamylammines, hydroxy or alkylamino substituted, a method for their preparation and pharmaceutical and veterinary compositions containing them.

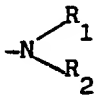
More particularly, the invention concerns compounds of general formula I



(I)

wherein:

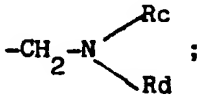
-X is OX or



wherein R_1 and R_2 being the same or different are linear or branched C_1-C_6-alkyl, C_3-C_6 cycloalkyl, cyclopropylmethyl, benzyl, hydroxyethyl, chloroethyl or groups R_1 and R_2 taken together with the nitrogen atom, are a piperazin-1-yl, 4-N-acetyl-piperazin-1-yl, N-methyl-piperazin-1-yl or aziridinyl residuate;

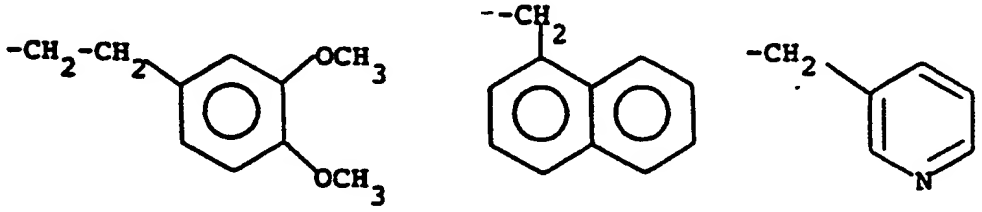
-R is selected in the group of hydrogen, C_1-C_4-linear or ramified alkyl, cyano or carboxyl esterified group;

-A and B being the same or different are selected in the group of hydrogen, C_1-C_4-linear or branched alkyl, C_1-C_2-alkoxy, halogen, 1-imidazolyl or a group of formula



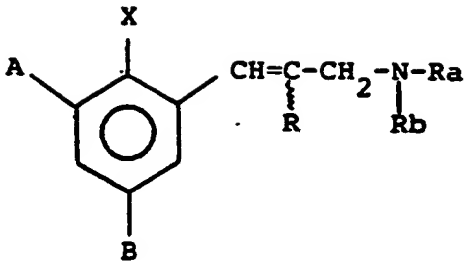
;

-Ra, Rb, Rc and Rd, which are the same or different, are selected in the group of C_1-C_4-linear or branched alkyl, C_3-C_6-cycloalkyl, cyclopropylmethyl, hydroxyethyl, chloroethyl, groups of formula

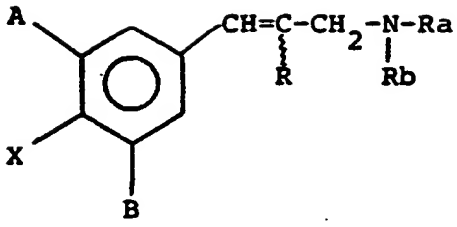


or the substituents of an amino disubstituted group, taken together with the nitrogen atom represent a saturated or unsaturated nitrogen heterocyclic ring;

-with the condition that the substituent X and the propenyl chain will be in ortho and para positions, and that the substituents A and B will be in the free orto and para positions of the ring, as specified in formulae Ia and Ib:



(Ia)



(Ib)

Specific examples of saturated or unsaturated nitrogen heterocyclic rings are: morphol-1-yl; pyrrolidin-1-yl, piperidin-1-yl, piperazin-1-yl, N-methyl-piperazin-1-yl, N-p-fluorophenyl-piperazin-1-yl, N-(phenylthiomethyl)piperazin-1-yl, N-(bisphenylmethyl)piperazin-1-yl, N-(bis-p-fluorophenylmethyl)piperazin-1-yl, aziridinyl, 2-carboxy-pyrrolidin-1-yl, 2-cyano-pyrrolidin-1-yl, 3-thiazolidinyl, 4-carboxy-3-thiazolidinyl.

Objects of the present invention are also salts of compounds of formula I with acids acceptable for pharmaceutical and veterinary use, and are also object of the present invention, like the geometric cis-and trans-isomers and mixtures thereof.

Examples of pharmaceutically acceptable salts include chlorhydrates, bromhydrates, iodidrates, alkyl and aryl sulphates, phosphates, sulphates, maleates, fumarates, succinates, tartrates, citrates and other salts of common use in the art.

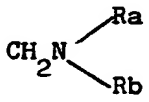
Some of the salts of the invention have sometimes particular advantages due to an increased solubility, an increased or lowered stability, possibility of crystallization, no disgusting taste, etc. , but all these respects aresecondary in comparison with the main pisyological action of the free base that does not depend on the kind of acid used.

In the formulae of the present invention the bond lines (~~~~) indicate that the relating substituents have no defined stoichiometrical identity, i.e. they indicate that the R group may be in cis-or trans-position with respect to the aromatic ring.

Preferred compounds of the invention are those wherein:

-X is OH;

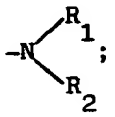
-A and B are hydrogen, methoxy, bromo, fluoro or



-R is hydrogen, cyano or methyl.

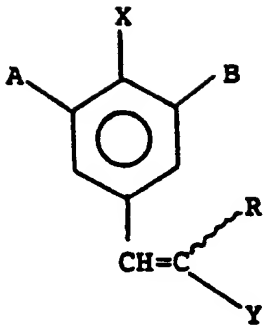
Particularly preferred compounds are those wherein:

-X is a group



-A and B are hydrogen, R is cyano, hydrogen or methyl.

Specific examples of preferred compounds of the invention are those of formula Ib

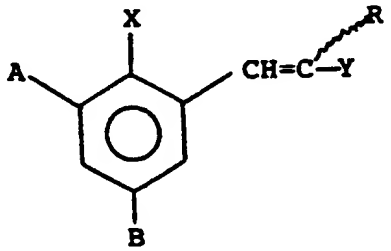


(Ib)

wherein the variants X, A, R, B and Y have the following meanings:

1) X = OH, A = OCH_3, R = H, B and Y = 1-morpholinomethyl;
2) X = OH, A = OCH_3, R = H, B = H, Y = 1-morpholinomethyl;
3) X = OH, A = OCH_3, R = H, B = OCH_3, Y = 1-morpholinomethyl;
4) X = OH, A = OCH_3, R = H, B and Y = 1-pyrrolidinylmethyl;
5) X = OH, A = OCH_3, R = H, B = OCH_3, Y = piperazinomethyl;
6) X = OH, A = OCH_3, R = H, B = OCH_3, Y = 3-thiazolidinylmethyl;
7) X = OH, A = OCH_3, R = H, B = 4-morpholinomethyl, Y = 1-prolinylmethyl;
8) X = OH, A= OCH_3, R = CH_3, B = OCH_3, Y = 1-morpholinomethyl;
9) X = OH, R = H, A, B and Y = 1-pyrrolidinomethyl;
10) X = OH, A = H, R = CN, B and Y = 1-morpholinomethyl;
11) X = OH, A = OCH_3, R = H, B = 1-pyrrolidinomethyl, 1 = 4-(bis-p-fluorophenylmethyl)-1-piperazinomethyl;
12) X = OH, A = OCH_3, R = H, B = 1-morpholinomethyl, Y = 4-(bis-p-fluorophenylmethyl)-1-piperazinomethyl;
13) X = OH, A = OCH_3, R = H, B = OCH_3, Y = 4-(bis-p-fluorophenylmethyl)-1-piperazinomethyl;
14) X = OH, A = OCH_3, R = CN, B = OCH_3, Y = [2-(3,4-dimethoxyphenyl)-ethyl]-methyl-aminomethyl;
15) X = OH, A = OCH_3, R = H, B and Y =4-(bis-p-fluorophenylmethyl)-1-piperazinomethyl;
16) X = OH, A and B = 1-pyrrolidinomethyl, R = H, Y = 4-(bis-p-fluorophenylmethyl)-1-piperazinomethyl;
17) X = OH, A and B = 1-morpholinomethyl, R = H, Y = 4-(bis-p-fluorophenylmethyl)-1-piperazinomethyl;
18) X = OH, A = OCH_3, R = H, B = Br, Y = 4-(bis-p-fluorophenylmethyl)-1-piperazinomethyl;
19) X = $N(Et)_2$, A = H, R = H, B = H, Y = 4-(bis-p-fluorophenylmethyl)-1-piperazinomethyl;
20) X + $N(Et)_2$, A = H, R = H, B = H, Y = 1-morpholinomethyl;
21) X = OH, A = OCH_3, R = H, B and Y = N-methyl-piperazinomethyl;
22) X = OH, A = OCH_3, R = H, B and Y = N-p-fluorophenyl-piperazinomethyl;
23) X = OH, A = OCH_3, R = H, B and Y = N,N-diethanolaminomethyl;
24) X = OH, A = OCH_3, R = H, B and Y = N,N-di-(2-chloroethyl)aminomethyl;
25) X = OH, A = B = 1-pyrrodilinomethyl, R = H, Y = 1-prolinylmethyl.

Examples of preferred compounds of formula Ia



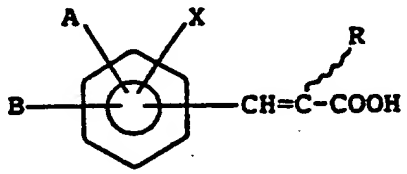
(Ia)

are those wherein th variants A, B, X, R and Y have the following meanings:

1) X = OH, A = H, B = F, Y = $-CH_2-N(Et)_2$, R = H;
2) X = OH, A = OCH_3, B = H, Y = 1-morpholinomethyl, R = H;
3) X = OH, A = OCH_3, B = Y = 1-morhplinomethyl, R = H;

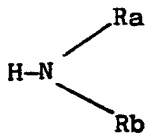
4) X = OH, B = F, A = Y = 1-morpholinomethyl, R = H;
5) X = OH, A = OCH_3, B = H, R = H, Y = 4-(bis-p-fluorophenylmethyl)-1-piperazinomethyl;
6) X = OH, A = OCH_3, R = H, B = Y = 4-(bis-p-fluorophenylmethyl)-1-piperazinomethyl;
7) X = OH, A = OCH_3, B = 1-morpholinomethyl, R = H, Y = 4-(bis-p-flu rophenylmethyl)-1-piperazinomethyl;
8) X = OH, A = B = 1-morpholinomethyl, R = H, Y = 4-(bis-p-fluorophenylmethyl)-1-piperazinomethyl;
9) X = $N(Et)_2$, A = B = R = H, Y = 4-(bis-p-fluorophenylmethyl)-1-piperazinomethyl;
10) X = OH, A = OCH_3, R = CH_3, B = Y = 1-morpholinomethyl;
11) X = OH, A = Y = 1-morpholinomethyl, B = OCH_3, R = H;
12) X = OH, A = Y = 1-morpholinomethyl, B = OCH_3, R P H;
13) X = OH, A = OCH_3; B = Br, Y = 1-morpholinomethyl, R = H;
14) X = OH, A = OCH_3, B = 1-imidazolyl, Y = 1-morpholinomethyl, R = H;
15) X = OH, A = OCH_3, B = R = H, Y = N-methylpiperazinomethyl;
16) X = OH, A = OCH_3, B = R = H, Y = N-2-hydroxyethyl-1-piperazinomethyl;
17) X = OH, A = OCH_3, B = R = H, Y = N-methyl-N-cyclohexylaminomethyl;
18) X + OH, A = Y = N,N-di(2-chloroethyl)-aminomethyl, B = R = H.

Compounds of the present invention are prepared by reacting an acid of formula II or one of its salts



(II)

wherein A, B, X and R are as above defined, with formaldehyde and a secondary amine of formula III



(III)

wherein Ra and Rb are as above defined. Formation of cinnamylamines substituted by reaction of cinnamic acids with formaldehyde and amines has bever been described up to now, and it is thus object of the present invention.

Reaction of acids II with formaldehyde and amines III is carried out by dissolving in suitable solvent formaldehyde and amine III generally in equimolecular quantities or using a molar excess of 2:1 or 3:1 of formaldehyde with respect to amine, together with such a quantity of acid II that the rate between moles of acid II and moles of amine III is included between 1:1:1 and 1:6. The resulting solution is then kept at a temperature ranging from room temperature and the solvent's reflux temperature. Suitable solvents for effecting the reaction include water, aqueous solutions of alkaline bicarbonates (such as $LiHCO_3$, $NaHCO_3$, $KHCO_3$), alcohols that can be mixed with water (such as ethanol, methanol, propanol and isopropanol), dimethoxyethane, tetrahydrofurane, diglime and mixtures thereof.

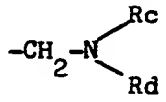
When the reaction is carried out in water or in aqueous solutions of alkaline bicarbonates, the reaction temperature ranges from room values and 50°C, but generally it is carried out at room temperature. In these conditions reaction time ranges from few minutes to 12 hours, but generally, the reaction is completed in 30'.

When the reaction is carried out in alcohols or ethers,or mixtures thereof with water, reaction temperature may vary from room values to the solvent's reflux temperature, but generally the reaction is carried out at 75°C. Reaction time ranges from a few minutes to 24 hours, but normally reaction is completed in two hours.

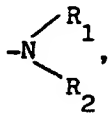
Experimental conditions used in reaction of acids II with formaldehyde and secondary amines III to give compounds of formula I are the same as for reaction of aminomethylation of phenols,that on its turn is a typical example of Mannich reaction. When the reaction is carried out using as starting material acids II wh r in X is OH and at least one of A and B is hydrog n, it is possible, by varying quantities of reagents

and experimental modalities, to make the reaction produce compounds I of different structure. When, for example the reaction is carried out on an acid of formula II wherein A and B are different from hydrogen, the molar ratio between amine III and acid II necessary to complete reaction varies from 1:1 to 1:5:1. Generally the reaction is completed utilizing a 10% molar excess of amine with respect to the acid.

When the reaction is carried out using as starting material an acid II in which at least one of A and B is hydrogen and X is OH, it is possoble, if desired, to avoid aminomethylation of aromatic ring, using equimolecular quantities of acid II, amine III and formaldehyde, and adding slowly the formic aldehyde to the solution of aicd II and amine III. It is used as starting material an acid of formula II wherein at least one of A and B is hydrogen, with the intention to obtain products of formula I from the reaction, wherein at least one of A and B is

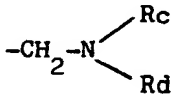


and Rc and Rd are the same as Ra and Rb, the reaction itself is carried out using an excess of formaldehyde and amine III with respect to acid II in a ratio varying from 3:1 to 6:1. When the reaction is carried out using acids of formula II as starting material, wherein X is

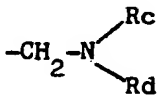


and R_1 and R_2 are as above defined, it is preferably used a molar excess of 10% of amine III.

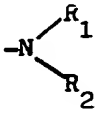
Acids of formula II wherein A and B are different from



are known products and they are prepared following known methods. In particular, acids of formula II wherein A and B are different from

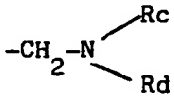


and X is OH, are prepared in accordance with J.F.E. Dupin and J. Chenault in Synthetic Communication, Vol. 15 (7), pages 581-586, 1985. Compounds of formula II wherein X is

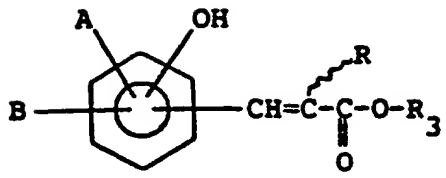


are prepared according to Gensler and Berman, in J. Am. Chem. Soc., Vol. 80, pages 4949-4954, 1958.

Compounds of formula II wherein X is OH and at least one of A and B is

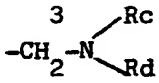


are obtained by alkaline hydrolysis from esters of formula IV



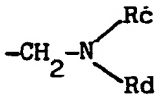
(IV)

wherein R is as above defined, but it is different from esterified carboxyl, R_3 is methyl or ethyl and one of A and B is a group of formula

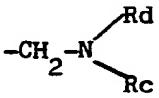


wherein Rc and Rd are as above defined.

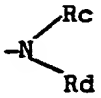
If desired, acids of formula II wherein at least one of A and B is



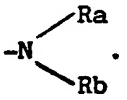
may be reacted without being isolated under form of alkaline or alkaline-earth salts with formaldehyde and a secondary amine of formula III to give compounds of formula I wherein at least one of A and B is



while the other is as above defined and wherein the amino group



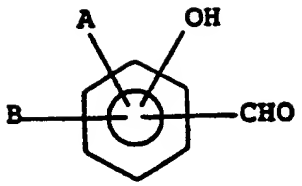
may be different from aminogroup



Hydrolysis reaction of esters of formula IV is effected in aqueous alcohol solutions such as methanol, ethanol, isopropanol in presence of a molar excess of an alkaline or alkaline-earth hydroxide, for example NaOH, KOH, $Mg(OH)_2$, $Ca(OH)_2$ or mixtures thereof.

The molar excess of alkaline or alkaline-earth hydroxyde with respect to ester varies from 2:1 to 4:1. The reaction is carried out at temperatures varying from room temperature to the solvent's reflux remperature. Reaction times range from few hours to 48 hours. Generally the reaction is executed in an aqueous ethanol solution at 50°C using a molar excess of NaOH of 2:1 with respect to ether of formula IV and the reaction is usually completed in 4 hours.

Esters of general formula IV, wherein R is CN are prepared by reacting the aldehydes of general formula V



(V)

wherein A and B are as above defined, with ethyl cyano-acetate according to Beilstein 10 : 520.

Finally, esters of general formual IV wherein R is C_1-C_4-alkyl are prepared by reaction of an aldehyde of formula V with a stabilzed ylide of formula VI

R- CH(=$P\phi_3$) -$COOR_3$ (VI)

wherein R and R_3 are as above defined.

Reaction of an aldehyde of formula V with stabilized ylides VI is a typical Wittig reaction. It is carried out in presence of molar quantities quite similar to reagents V and VI in a temperature ranging from -30°C to the solvent's reflux temperature but preferably between -10°C and room temperature, and in solvents such as tetrahydrofurane, dimethoxyethane, dimethylformamide, dimethylsulphoxide, benzene, toluene or mixtures thereof. The stabilized ylides are otabined by means of action of bases, such as sodium-hydroxide, etc. on the corresponding phosphonium salt.

The aldehydes of formula V are products are products known in literature and may be obtained following known methods.

Particularly, the preparation of aldehydes of formula V is described in the patent appln. No.21433 A/86 of 7th Aug.1986.

When compounds of the invention are administered by oral, intraperitoneal and intravenous route to rats and mosues, they show low toxicity, with LD_{50} after oral administration included between 0.3 g and 0.9 g/Kg.

It is described a reduced production of malondialdehyde after stimulation with H_2O_2 of heritrocyte membranes of rats incubated with compounds of the invention.

When administered by oral and intraperitoneal route, compounds of the invention further protect mouses from sudden death induced by administration (in bolus) or arachidonic acid or mixtures of ADP and collagene.

Compounds of the invention are moreover able to protect cell membranes from oxidation,thus preventing lypoperoxidation phenomena.

Compounds of the invention are moreover able to interfer with intra-and extracellular oxidation processes, thus a control of the same is enabled and they act as "radical scavenger" of free radicals.

Trimetazidine, for instance, is a molecule provided with anti-angina activity, but without calcium-blocking activity, and its mechanism of action has not yet been well defined.

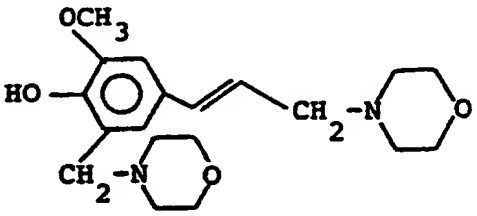
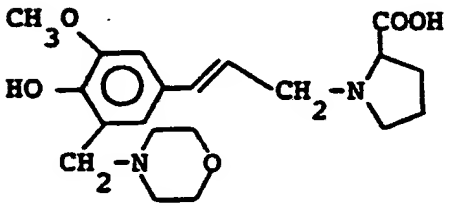
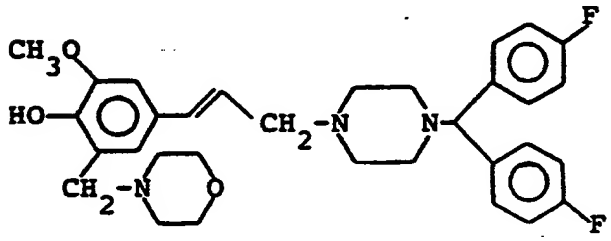
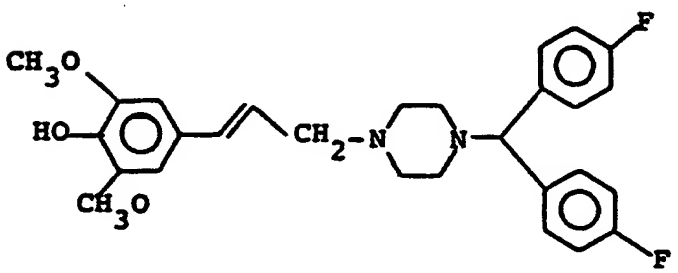
Recent studies show that its pharmacological activity is due to a metabolite of the substance (probably having a phenolic nature) that is able to protect cell membranes from damages caused by oxygen free radicals. Cynnarizine and flunarizine are substances with cinnamylamine structure, vinyl analogues or trimatazidine, that are active as vasodilators and calcium blocking agents, and used as brain vasodilators, with protecting effect on brain. Since it seems that generation o free radicals, together with the sub sequent peroxidative degeneration of cell-membrane is responsible for the brain-ischemic damage, the anti-oxidation or as "radical-scavenger" activity of flunarizine has been valued in vitro (Arch. Int. Pharmacology, 272 , 283, 1984). Flunarizine resulted to be very active as "radical scavenger", thus differing from other calcium antagonists, like nifedipine, that, on their turn, are completely lacking of brain-protecting activity.

Successively it has been found that compounds of the invention have a high anti-oxidation or free-radical scavenger activity, comparable and sometimes higher than that of known anti-oxidation agents, like α-tocopherol and ascorbic acid.

Potential as "radical scavengers" of compounds of the invention is chemically demonstrable (see for ex. A Mellors et al, J. Biol. Chem., 241, 4353, 1966) by measuring the absorption decrease to 510 nm. of solutions 0.1 mM of a steady radical, such as diphenyl-p-picryl-hydrazile.

According to R. Rubo t al, Arch. Int. Pharmacol., 272, 283, 1984 values of activity are expressed as $IC_{0,2}$ (cuvette concentration of xamined substance (M) that is able to reduce of 0.2 units of optical density, absorption of a solution 0.1 mM of diphenylpicrylhydrazile).

The table reports values of $IC_{0,2}$ for some of the compounds of the invention, for some known anti-oxidation agents, ascorbic acid, hydroquinone and for a known cinnamylammine, flunarizine.

Compound	$IC_{0,2}$
	8
	6
	13
	7
Hydroquinone	9,5
Ascorbic acid	11,5
Flunarizine HCl	160

Data reported in the Table indicate clearly that some of the compound have an anti-oxidation activity in vitro comparable or higher than that of ascorbic acid and hydroquinone.

Compounds of the inv ntion hav also a radical scavenger and anti-oxidation activity 10 times superior to that of flunarizine whose anti-oxidation activity seems to be bound to brain protecting action of flunarizine.

Compounds of the present invention are able to modify intra-and extracellular availability of CA^{++} ions in mammals biological liquids.

For this reason compounds of the invention are therapeutically useful to control tissue metahbolitic processes, aiming at the regulation of contractions of smooth and striated muscles.

Utility of compounds of the invention includes also control "in vivo" of enzymatic processes depending on cellular availability of Ca^{++} ions, as for example inhibition and/or activation of phospholipase, phosphodiesterase, collagenase, elastase, etc. Compounds of the invention are particularly useful to control intra-and extracellular movements of electrolites (Ca^{++}, Na^{+}, K^{+},Mg^{++}) that regulate deformation of cellular components of blood, such as piastrines, leucocites, heritrocites, thus cooperating to blood viscosity regulation.

When tested "in vivo" compounds of the invention have a secretolitic effect on bronchial mucus, as shown by red-phenol and fluoresceine sodium salts tests on rats and mouses.Compounds of the invention moreover modify physical (viscosity and volume) and biochemical parameters of mucus produced by bronchitic rabbits.

From the above arguments it is evident that compounds of the invention are useful in therapy as tissue protectors, anti-thrombotic, anti-oxidation, mucolitic agents, etc.

To reach the desired effects in human and veterinary therapy, compounds of the invention may be administered parenterally, for ex. as intravenous, hypodermic and intramuscular injection, as infusion, or by oral route. Compounds may be administered to patient under pure form or as pharmaceutical compositions.

Opportune pharmaceutical compositions may be realized in accordance with known techniques, as described for ex. in "Remington's Pharmaceutical Sciences Handbook",Hack Publishing Co.U.S.A.

When compounds of the invention are used as antihypertensive agents, dosage will vary according to seriousness of hypertension and route of administration.

Quantity of active principle administered by oral route may range from 0.01 mg/die to 100 mg/Kg/die, preferably from 0.5 mg/die to 10 mg/Kg/die.

Quantity of active principle administered by perenteral route may contain, for ex., from 0.001 mg/die to 10 mg/Kg/die, preferably from 0.01 mg/die to 1 mg/kg/die.

A dose for oral administration may contain, for example, from 0.1 to 1000 mg of active principal.

Compounds of the invention may be administered once a day, but more spaced and/or repeated administrations may be convenient in some cases and may vary according to conditions of the patient, routes of administration and dosages used. In the present occasion the word "patient" means hot-blooded animal,man included.

For oral administration compound may be formulated in solid or liquid preparations as capsules,pills, tablets, suspensions or emulsions.Solid unit dose may be a hard or soft gelatine capsule containing lubricants or inert eccipients such as lactose, saccharose or amide.

Compounds of the invention may also be formulated as tablets utilizing conventional eccipients like lactose, saccharose, amide, gelatine, alginic acid,stearic acid, magnesium stearate,etc.

For parenteral administration compounds may be prepared in injectable formulations by melting or suspending them in physiologically acceptable diluents, with a vehicle that can be sterile water or oil, with or without adding other eccipients.Oils employed may be of vegetable, animal, mineral or synthetic origin, like peanut, soya and mineral oil.Generally, as a vehicle for injectable solutions it is possible to utilize water, aqueous solutions of mineral salts, aqueous solutions of dextrose or other sugars,ethanol glycols such as propylene or polyethylene glycols.

Compounds may als be administered by oral route, as suppositories, mixed with conventional vehicles as for example cocoa butter, wax, polyvinylpyrrolidone or polyoxyethylenglycole or derivatives thereof.

The preferred administration route for compounds of the invention is the oral route.

The invention is further described but not limited by the following examples.

EXAMPLE 1

A solution of methyl 4-hydroxy-5-methoxy-3-(1-pyrrolidinylmethyl)-cinnamate (2.77 g) and sodium hydrate (0.76 g) in 95% ethanol (60 ml) and water (10 ml) is heated to reflux for 90'. After cooling at 0°C, pH of the solution is brought to 7.2 with concentrated hydrochloric acid (2.8 ml) and formaline at 37% (0.92 ml) is added.The solution is warmed at reflux temperature and successively added in 40:50' by a solution of 1-[bis-(p-fluorophenyl)methyl]piperazine (3.28 g) in ethanol (50 ml).

The reflux is continued for one hour. Successively the solvent is evaporated under reduced pressure and the obtained resi duate is dissolved in ethyl acetate (80 ml), the resulting suspension is filtered and the filtrate is anidrified on Na_2SO_4. The organic phase is concentrated and the residuate is chromatographated on SiO_2; eluent ethyl acetate/n-esane/triethylamine 9/3/0.3. G. 2.6 of 4-[bis-(p-fluorophenyl-methyl]-[[4-hydroxy-5-methoxy-3-(1-pyrrolidinylmethyl)]-cinnamyl]-piperazine are obtained that are dissolved in ethyl ether (25 ml) and treated with a solution 8.4 N of HCl in isopropanol (3.2 ml) to give 2.74 g of the corresponding exahydrate trichlorhydrate; m.p.174-188°C.

EXAMPLE 2

Using in procedure of Example 1 the opportunely substituted cinnamic esters, or the opportune amines, the following compounds are prepared:

-4-[bis(p-fluorophenyl)-methyl]-1-[[4-hydroxy-5-methoxy-3-(4-morpholinylmethyl)]-cinnamyl]-piperazine, 2HCl, 2.5 H_2O, m.p. (decompones);

-4-[bis(p-fluorophenyl)-methyl]-[[2-hydroxy-3-methoxy-5-(4-morpholinylmethyl)]-cinnamyl]-piperazine trichlorhydrate; m.p.177-190°C alteration; 200-204°C decomposition;

-4-[bis(p-fluorophenyl)-methyl]-1-[[4-hydroxy-3,5-bis(4-morpholinylmethyl)]-cinnamyl]-piperazine; m.p.148-150°C; bitartrate, bihydrate; m.p. 90-93°C;

-4-[bis(p-fluorophenyl)-methyl]-1-[[4-hydroxy-3,5-bis(4-pirrolidinylmethyl)]-cinnamyl]-piperazine; m.p.131-133°C, tetrachlorhydrate monohydrate; m.p.196-200°C;

-4-[bis(p-fluorophenyl)-methyl]-1-[[2-hydroxy-3?5-bis(4-morpholinylmethyl)]-cinnamyl]-piperazine; NMR ($CDCl_2$, TMS): δ = 3.20, d, 2H (Ar-CH=CH-$\underline{CH_2}$-N); δ = 4.25, s, 1H (N-$\underline{CH}$-Ar_2); δ = 6.11-7.65,m, 12H (aromatic hydrogens + -$\underline{CH=CH}$-);

-1-[[4-hydroxy-5-methoxy-3-(4-morpholinylmethyl)]-cinnamyl] proline; sesquihydrate; m.p.70-72°C (decompones);

-N-[[4-hydroxy-5-methoxy-3-(4-morpholinylmethyl)]-cinnamyl]-N-methyl-cycloexylamine; NMR ($CDCl_2$; TMS): δ 0.82-2.1, m,11H, (-N-cycloexyl);δ=2.2, s, 3H (-N-CH_3); δ = 3.15,d,2H (CH=CH-$\underline{CH_2}$):δ = 5.8-7.2, m, 4H (aromatic + -CH=CH-);

-N-[[4-hyroxy-5-methoxy-3-(4-morpholinylmethyl)]-cinnamyl]-N-methyl-omoverartrilamine; NMR ($CDCl_3$; TMS):δ = 2.35,s,3H (N-CH_3); δ = 3.18,d,2H (-CH=CH-$\underline{CH_2}$-N-):δ = 5.70-6.90, m,7H (aromatic+-CH=CH).

EXAMPLE 3

A solution of 1-[bis-(p-fluorophenyl)-methyl]-piperazine (g 0.28) is added in a period of 15' to a boiling solution of 4-hydroxy-5-methoxy-3-[4-[bis-(p-fluorophenyl)-methyl]-piperazin-1-yl-methyl]-cinnamic acid (0.44 g) and formaline 37% (0.08 ml) in ethanol (5 ml). When adding is completed, the heating is prosecuted for 90'. Successively,the solvent is evaporated under a reduced pressure and the obtained residuate is dissolved in ethyl acetate (15 ml).After washing with $NaHCO_3$ 5% (5 ml) and with a saturated solution of NaCl the organic phase is anidrified (Na_2SO_4) and the solvent is evaporated under reduced pressure. The obtained residuate is purified by chromatography on column (SiO_2; eluent ethyl acetate /n-esane/TEA 10/10/1). G. 0.45 of 4-[bis-(p-fluorophenyl)-methyl]-1-[[4-hydroxy-5-methoxy-3-[4-bis-(p-fluorophenyl)-methyl]-piperazin-1-yl-methyl]-cynnamyl]-piperazine are obtained, and when they melted in ethyl acetate (10 ml) and heated with a solution 8.4 N of HCl in isopropanol (0.6 ml) they give 0.52 g of the corresponding bihydrate tetrachlorhydrate; m.p.162-170°C (decomposition).

EXAMPLE A

A solution of 4-hydroxy-3-methoxy-cinnamic acid (1.55 g) and N-methylpiperazine (2.21 ml) in water (30 ml) is added with formaline 37% (1.62 ml). It is left at room temperature for 12 hours. Successively 5% $NaHCO_3$ (10 ml) is added and the solution is extracted with chloroform. The organic extracts are put together and washed with NaCl saturated solution (10 ml), anidrified (Na_2SO_4) and the solvent is evaporated under a reduced pressure.

The obtained residuate is crystallized by ethyl ether/ethyl acetate. G. 2.49 of 4-methyl-1-[[4-hydroxy-5-methoxy-3-[methyl-piperazin-1-yl-methyl]-cinnamyl]-piperazine,m.p.118-121°C.

EXAMPLE 5

A solution of 4-hydroxy-3-methoxy-cinnamic acid (7.76 g) morpholine (8.78 g) and formaline 37% (8.11 ml) in ethanol (50 ml) is heated to reflux for an hour. The solvent is thus separated under reduced pressure and the obtained residuate is partioned between $NaHOC_3$ 5% (20 ml) and ethyl acetate (100 ml). The organic phase isseparated and the aqueous one is re-extracted with ethyl acetate (2 x 70 ml). Organic extracts together are washed with NaCl saturated solution (20 ml), anidrified (Na_2SO_4) and the solvent is evaporated under a reduced pressure. The obtained residuate is crystallized from ethyl ether (200 ml). G. 11.08 of 4-[[4-hydroxy-5-methoxy-3-(4-morpholinylmethyl)]-cinnamyl]-morpholine,m.p.101-103°C, are obtained.

EXAMPLE 6

Using in the procedures of examples 3, 4, 5 the cinnamic acids opportunely substituted and the opportune amines, the following compounds were obtained:

-4-[[2-hydroxy-3-methoxy-5-(1-morpholinylmethyl)]-cinnamyl-morpholine, m.p.111-112°C;

-4-[[2-hydroxy-5-methoxy-3-(1-morpholinylmethyl)]-cinnamyl]-morpholine bichlorhydrate bihydrate,m.p.135-140°C (decompones;

-4-[[4-hydroxy-3,5-dimethoxy]-cinnamyl]-morpholine monochlorhydrate, m.p.178-182°C;

-4-[[2-hydroxy-5-fluoro-3-(1-morpholinylmethyl)]-cinnamyl-morpholine, m.p.162-164°C;

-1-[[4-hydroxy-5-methoxy-3-(1-pyrrolidinylmethyl)]-dinnamyl]-pyrrolidine bichlorhydratesesquihydrate, m.p.95°C (decompones);

-1-[[4-hydroxy-3,5-bis-(1-pirrolidinylmethyl)]-cinnamyl]-pirrolidine hdyrate, m.p.79°C (decompones);

-4-[bis-(p-fluorophenyl)-methyl]-1-[[4-hydroxy-3,5-dimethoxy]-cinnamyl]-piperazine bichlorhydrate emihydrate,m.p.213-216°C;

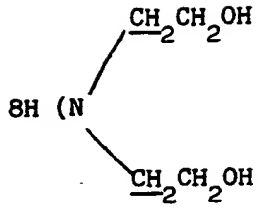
-4-[bis-(p-fluorophenyl)-methyl]-1-[[2-hydroxy-3-methoxy-5-[bis-(p-fluorophenyl)-methyl]-piperazine-1-yl-methyl]]-cinnamyl]-piperazine tetrachlorhydrate bihydrate, m.p.184.7-186.6°C;

-4-(p-fluorophenyl)-1-[[4-hydroxy-5-methoxy-3-[4-(p-fluorophenyl)-piperazine-1-yl-methyl]]-cinnamyl]-piperazine m.p.149-152°C;

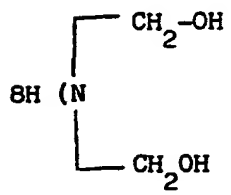
-3-[(4-hydroxy-3,5-dimethoxy)-cinnamyl]-piperazine, m.p.120-121°C;

-N-[[2-hydroxy-5-fluoro-3-(diethylaminomethyl)]-cinnamyl]N,N-diethylamine; NMR ($CDCl_2$; δ TMS); δ 1,10, t,12H ($\underline{CH_3}$-CH_2-N-CH_2-$\underline{CH_3}$) 2.62,q,8H (CH_2-$\underline{CH}$ $_2$-N-$\underline{CH_2}$-CH_3); δ3,31, d,2H (A_2-CH=CH-$\underline{CH_2}$-N); 3.70, s,2H, (Ar-$\underline{CH_2}$-N-);δ 5.9-7.28,m,4H (aromatics + -CH=CH-);δ 10.22, s, 1H (-O-H);

-N-[[4-hydroxy-5-methoxy-3-[bis-(2-hydroxyethylamino)-methyl]]-cinnamyl]-diethanolamine; NMR ($CDCl_2$, TMS); 2.68, y,



8H (N); δ 3.28,d,2H (–CH=CH–CH_2–N); δ 3.6, t,



8H (N); δ 4.25, s, 2H (A–CH_2–N); δ 5.70–6.99, m,

4H (aromatics = –CH=CH–);

-4-(3,5-dibromo-2-hydroxy)-cinnamyl]-morpholine;
-4-[bis-(p-fluorophenyl)-methyl]-1-[[3-bromo-4-hydroxy-5-methoxy]-cinnamyl]-piperazine;
-4-[(5-bromo-2-hydroxy-3-methoxy)-cinnamyl]-morpholine;
-4-[[2-hydroxy-5-(1-imidazollyl)-3-methoxy]-cinnamyl]-morpholine.

EXAMPLE 7

A suspension of 3,5-dimethoxy-4-hydroxy-cinnamic acid (4.48 g) in water (50 ml) is added with N-formyl-piperazine (2.5 ml). The obtained solution is added at 20°C with a formaline 37% solution (3.9 ml) in water (15 ml) in a period of 30'. After 12 hours at room temperature, the reaction mixture is poured in an excess of $NaHCO_3$ 5%, saturated with NaCl and extracted with chloroform (5 x 30 ml). The organic extracts together are anidrified (Na_2SO_4) and the solvent is evaporated under a reduced pressure. The obtained residuate is melted in methanol (90 ml), concentrated hydrochloric acid (8 ml) is added and the solution is heated to reflux for 4 hours. After a night at room temperature the compound is diluted with ethyl ether (90 ml). By cooling at 0°C a solid of separation is obtained, which is separated by filtration under nitrogen atmosphere and washed with ethyl ether. G. 3.5 of 1-[4-hydroxy-3,5-dimethoxy)-cinnamyl]-piperazine bichlorhydrate monohydrate, m.p. 168-171°C are obtained.

EXAMPLE 8

Using in procedure of example 7 opportunely substituted cinnamic acids and N-formyl-piperazine, the following compounds are obtained:
-1-[(5-bromo-2-hydroxy-3-methoxy)-cinnamyl]-piperazine;
-1-[(2-hydroxy-5-(1-imidazolyl)-3-methoxy-cinnamyl]-piperazine;
-1-[(3-bromo-4-hydroxy-5-methoxy)-cinnamyl]-piperazine.

EXAMPLE 9

A boiling solution of 2-hydroxy-3-methoxy-cinnamic aicd (13.6 g) and morpholine (8.52 ml) in n-propanol (130 ml) is added slowly with a formaline 37% solution (7.94 ml) in water (20 ml). When adding is finished the compound is left to reflux for 2 hours and then at room temperature for one night. The solvent is evaporated under reduced pressure, and the obtained residuate is dissolved in ethyl acetate (130 ml) and washed with $NaHCO_3$ 5% (2 x 20 ml) and with NaCl saturated solution (30 ml). The organic phase is anidrified (Na_2SO_4) and the obtained residuate after evaporation of the solvent under reduced pressur , is purified by chromatography on column (SiO_2, ethyl acetate / TEA 20/1).

G . 11.28 of 4-[(2-hydroxy-3-methoxy)-cinnamyl]-morpholine m.p.139-141°C are obtained, they are melted in ethyl acetat and heated with a 8.4 N solution of HCl in isopropanol to give g 11.06 of the corresponding monochlorhydrate, m.p.187.7)188.6°C.

EXAMPLE 10

Using in procedure of example 9 the cinnamic acids opportunely substituted and the opportune amine, the following compounds were prepared:
-4-[(4-hydroxy-3-methoxy)-cinnamyl]-morpholine monochlorhydrate, m.p.182-185°C;
-N-[(2-hydroxy-5-fluoro)-cinnamyl]-N,N-diethylamine monochlorhydrate, m.p.140-147°C;
-4-[bis-(p-fluorophenyl)-methyl]-1-[(2-hydroxy-3-methoxy)-cinnamyl]-piperazine, m.p.138-140°C bichlorhydrate monohydrate, m.p.217°C (decomposition);
-4-methyl-1-[(2-hydroxy-3-methoxy)-cinnamyl]-piperazine;
-4-(2-hydroxyethyl)-1-[(2-hydroxy-3-methoxy)cinnamyl]-piperazine;
-N-methyl-N-[(2-hydroxy-3-methoxy)-cinnamyl]-cycloexylamine.

EXAMPLE 11

A solution of 3,5-dimethoxy-4-hydroxy-α-methyl cinnamic acid (1.14 g) and morpholine (0.46 ml) is added with 37% formaline (0.43 ml). The solution is left for 18 hours at room temperature and then it is heated at 55°C for 2 hours. After cooling at room temperature an excess of $NaHCO_3$ is added and the compound is extracted with ethyl acetate (3 x 10 ml). organic extracts are set together, anidrified (Na_2SO_4) and the solvent is separated under reduced pressure.

G. 0.80 of 4-[[4-hydroxy-3,5-dimethoxy-α-methyl]-cinnamyl]-morpholine,m.p. 103-106°C are obtained.

EXAMPLE 12

Using in procedure of Example 11 opportunely substituted methyl cinnamic acids and morpholine, the following compounds are obtained:
-4-[[4-hydroxy-5-methoxy-3-(4-morpholinylmethyl)-α-methyl]-cinnamyl]-morpholine;
-4-[[2-hydroxy-3-methoxy-5-(4-morpholinylmethyl)-α-methyl]-cinnamyl]-morpholine.

EXAMPLE 13

A solution of α-cyano-4 hydroxy-cinnamic acid (1.89 g) and morpholine (2.87 g) in ethanol (40 ml) is added with formaline 37% (2.68 ml). The solution is heated to reflux for 7½ hours. After one night at room temperature, the solvent is separated under reduced pressure, the obtained residuate is dissolved in ethyl acetate (50 ml) and washed with $NaCOH_3$ (4 x 20 ml) and with NaCl saturated solution.The organic phase is anidrified (Na_2SO_4)and evaporated.

The residuate is crystallized from ethyl ether and successively recrystallized from ethanol (two times). G.0.48 of 4-[[4-hydroxy-3-(4-morpholinyl-methyl)-α-cyano]-cinnamyl]-morpholine, m.p.164.1-166°C are obtained.

EXAMPLE 14

Using in procedure of example 13 an opportunely substitued α-cyano cinnamic acid and the opportune amines, the following compounds are prepared:
-N-[[2-hydroxy-3)methoxy-α-cyano]-cinnamyl]-N-methyl-omoveratrilamine;
- N-[[2-hydroxy-3-methoxy-5-bromo-α-cyano]-cinnamyl]-N-methyl-omoveratrilamine;
-N-[[4-hydroxy-3,5-dimethoxy-α-cyano]-cinnamyl]-N-methyl-omoveratrilamine;
-N-[[4-hydroxy-5-methoxy-3-(4-morpholinylmethyl)-α-cyano]-cinnamyl]-N-methyl-omoveratrilamin ;
-N-[[2-hydroxy-3-methoxy-5-(4-morpholinylmethyl)-α-cyano]-cinnamyl]-N-methyl-omoveratrilamin .

EXAMPLE 15

A boiling solution of p-diethylamino cinnamic acid (4.0 g) and formaline (37%,2.94 ml) in ethanol (50 ml) is slowly added with a solutionof 1-[bis-(p-fluorophenyl)-methyl]-piperazine (5.68 g) in ethanol (50 ml). When adding is terminated, heating to reflux is prosecuted for two hours. Successively the solvent is evaporated under reduced pressure and the obtained residuate is dissolved in ethyl acetate (80 ml), washed with $NaHCO_3$ 5% (2 x 20 ml). The organic phase is then anidrified (Na_2SO_4) and the solvent is evaporated under reduced pressure. The obtained residuate is crystallized from isopropyl ether. G. 4.6 of 4-[bis-(p-fluorophenyl)-methyl]-1-(p-diethylaminocinnamyl)-piperazine,m.p.92-94°C are obtained.

EXAMPLE 16

Using in procedure of Example 15 dialkylamino - cinnamic acids opportunely substituted, and the opportune amines, the following compounds are prepared:
-4-(p-diethylamino-cinnamyl)-morpholine;
-4-[bis-(p-fluorophenyl)-methyl]-1-[o-diethylaminocinnamyl]-piperazine;
-4-hydroxy-1-[3,5-dibromo-2-diethylaminocinnamyl]-piperidine;
-4-hydroxy-N-[3,5-dibromo-2-diethylaminocinnamyl]-N-methyl-cyclohexylamine.

EXAMPLE 17

A solution of sodium hydrate (0.49 g) in water (16 ml) is added with portions of ethyl-4-hydroxy-3-(4-morpholinomethyl)-5-methoxy-cinnamate (1.35 g) and the resulting solution is heated to 45°C for 45'. Successively the solution is cooled at room temperature and pH is brought to 4.8 with HCl 2N, then L-proline methyl ester chlrohydrate (0.75 g) and successively formaline 37% (0.41 ml) are added.

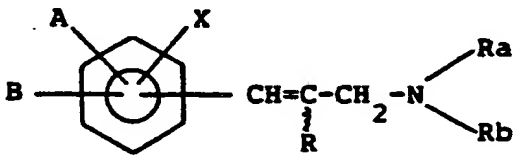
After 2 ½ hours at room temperature, $NaHCO_3$ is added to obtain a pH 7.5-8.0 and the solution is quickly extracted with chloroform (3 x 30 ml). The organic extracts together are washed with a NaCl saturated solution, anidrified (Na_2SO_4) and evaporated under reduced pressure.

G. 1.0 of 1-[[4-hydroxy-5-methoxy-3-(4-morpholinylmethyl)]cinnamyl]-L-proline methyl ester are obtained.

NMR ($CDCl_2$; TMS): δ = 1.59,2.28,m,4H (proline);δ = 3.01-3.02,d,2H (CH=CH-CH_2-N); δ =3,96,s,3H (-$COOCH_3$); δ = 6,20-6.81,m,4H (aromatics = -CH=CH-).

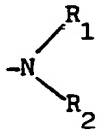
Claims

1. Compounds of formula I



(I)

wherein:
-X is OH or

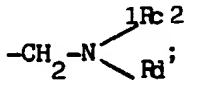


wherein R_1 and R_2 being the same or different are linear or branched C_1-C_6-alkyl, C_3-C_6-cycloalkyl, cyclopropylmethyl, benzyl, hydroxyethyl, chloroethyl or groups R_1 and R_2 taken together with the azote

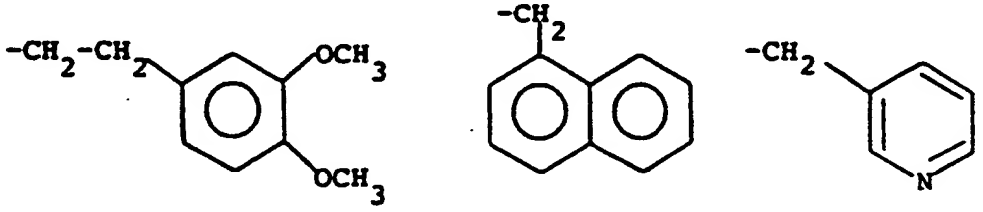
atom, are a piperazin-1-yl, 4-N-acetyl-piperazin-1-yl, N-methyl-piperazin-1-yl, N-methyl-piperazin-1-yl or aziridinyl residuate;

-R is selected in the group of hydrogen, C_1-C_4-linear or branched alkyl, cyano or carboxyl esterified group;

-A and B being the same or diff rent are selected in the group of hydrogen, C_1-C_4-linear or branched alkyl, C_1-C_2-alkoxy, halog n, 1-imidazolyl or a group of formula

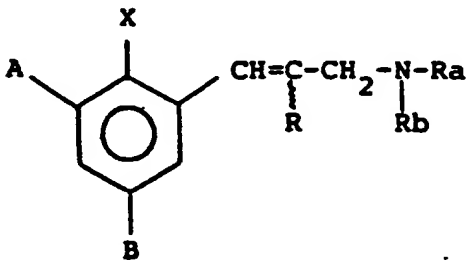


-Ra, Rb,Rc and Rd, that can be the same or different are selected in group of C_1-C_4-linear or branched alkyl, C_3-C_6-cycloalkyl, cyclopropylmethyl, hydroxyethyl, chloroethyl, groups of formula

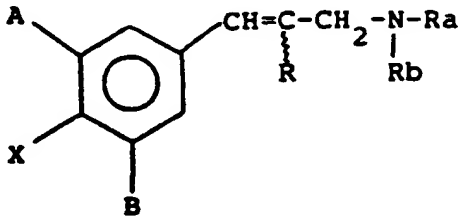


or the substituents of a disubstituted aminogroup taken together with the nitrogen atom represent a saturated or unsaturated nitrogen heterocyclic ring;

-with the condition that the substituent X and the propenyl chain are in orto or para position, and that the substituents A and B are in the other free orto and para positions of thering, as specified in formulae Ia and Ib:



(Ia)

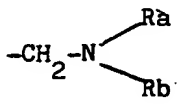


(Ib)

their non toxic salts, optical and geometrical isomers and mixtures thereof.

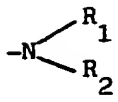
2. Compounds according to claim 1, wherein the saturated or unsaturated nitrogen heterocyclic ring is selected in the group formed by morpholin-4-yl, pyrrolidin-1-yl, piperdin-1-yl, piperazin-1-yl, N-methyl-piperazin-1-yl, N-p-fluorophenyl-piperazin-1-yl, N-(phenylthiomethyl)-piperazin-1-yl, N-(bis-phenylmethyl)-piperazin-1-yl, N-(bis-p-fluorophenylmethyl)-piperazin-1-yl, aziridinyl, 2-carboxy-pyrrolidin-1-yl, 2-cyano-pyrrolidin-1-yl, 3-thiazolidinyl, 4-carboxy-3-thiazolidinyl.

3. Compounds according to claims 1 and 2, wherein X is a hydroxy group, A and B or hydrogen, methoxy, bromo, fluoro, or a residuate of formula



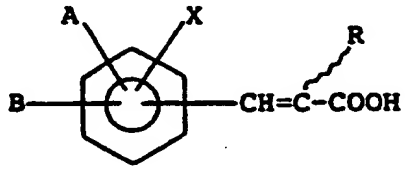
wherein Ra and Rb are the same as in claim 1.

4. Compounds according to claim 1 or 2, wherein X is a group of formula



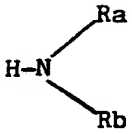
wherein R_1 and R_2 are as defined in claim 1, A and B areh ydrogen and R is cyano, hydrogen or methyl.

5. Process for preparation of compounds of claims 1-4 characterized in that an acid of formula II or its sodium or potassium salt



(II)

wherein A, B, X and R are as above defined, are reacted with formaldehyde and a secondary amine of formula III



(III)

wherein Ra and Rb are as above defined.

6. Process according to claim 5, characterized in that the reaction is carried out in solvents selected in the group formed by water, aqueous solutions of alkaline carbonates or bicarbonates, lower C_1-C_3-alcohols, dimethoxyethane, tetrahydrofurane, diglime and mixtures thereof.

7. Process according to claims 5 or 6, characterized in that molar rates between acid II and amine III are substantially equivalent.

8. Process according to claims 5 or 6 characterized in that an excess of formaldehyde and amine is used with respect to acid II that may range from 3:1 to 6:1.

9. Pharmaceutical compositions containing as an active principle at least one of compounds of claims 1-4 and a pharmaceutically acceptable vehicle.

10. Compounds according to claims 1-4 used as therapeutical agents.

11. Compounds according to claims 1-4 used as radical "scavengers",anti-oxidation, tissue protecting, antithrombotic and mucolithic agents.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 87 11 4175

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	CHEMICAL ABSTRACTS, vol. 77, no. 21, 20th November 1972, page 402, abstract no. 139538q, Columbus, Ohio, US; H. BOEHME et al.: "Alpha-halo amines. 39. Reaction of substituted cinnamic acids, esters, and aldehydes with alpha-halo amines", & ARCH. PHARM. (WEINHEIM, GER.) 1972, 305(8), 610-14	1,5,9-11	C 07 C 91/30 C 07 C 93/14 C 07 C 101/72 C 07 C 121/80 C 07 D 295/08 C 07 D 295/12 C 07 D 295/14 A 61 K 31/00
X	ARZNEIMITTEL FORSCHUNG, vol. 33, no. 8, 1983, pages 1142-1151, Aulendorf, DE; W. MEULDERMANS et al.: "Excretion and metabolism of flunarizine in rats and dogs" * Page 1143 *	1,9-11	
Y	US-A-2 831 864 (E.R. BOCKSTAHLER) * Column 1, lines 11-36 *	1,9-11	
Y	EP-A-0 187 639 (KANEBO) * Claims *	1,9-11	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 C 91/00
C 07 C 93/00
C 07 C 101/00
C 07 C 121/00
C 07 D 295/00
A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	04-01-1988	MOREAU J.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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